REMARKS

In the Advisory Action dated May 11, 2007, the Examiner indicated that the Amendment file April 16, 2007 would be entered and that Applicant's reply had overcome the rejection of the claims under 35 U.S.C. 102(e) based on Minden et al. Applicant respectfully requests reconsideration of this application in view of the amendments and remarks made herein.

Claims 1-11, 13-14, 17-18, 21 and 24-27 are pending. Claims 22, 23 and 28-49 are canceled. Claims 12, 15-16, and 19-20 are withdrawn from consideration with the understanding that said claims will be reintroduced upon allowance of a generic claim.

1. Summary of the Invention

The present invention relates to a method for proteomic analysis of a heterogeneous sample of peptides, or protein or peptide fragments. The key features of the method of the present invention are that the heterogeneous sample is separated into discrete *heterogeneous* classes, and that the *mass* and *abundance* of peptides, or protein or peptide fragments *in those heterogeneous classes* are determined. As explained below, there is nothing in the prior art that teaches, or even suggests, that one of skill in the art should analyze a heterogeneous sample of peptides, or protein or peptide fragments by separating that sample into discrete *heterogeneous* classes, and then determining the *mass* and *abundance* of peptides, or protein or peptide fragments, in those heterogeneous classes. Moreover, as explained further below, this combination of method features provides important advantages to the user, such that one can generate a profile of complex protein samples using relatively simple arrays with a lower number of binders.

As disclosed in the specification, one of the disadvantages of prior art methods for proteomic analysis was the very large numbers of protein-specific binders required to achieve this analysis (see, page 3 lines 15-22). In general, the prior art methods for protein sample

analysis used "binders" (i.e. molecules with a specific binding affinity) designed to be specific for individual proteins (or fragments derived therefrom) in a sample and so, for example, in order to analyze a sample of 2000 different proteins one needed to individually isolate each of those 2000 proteins in advance, generate a specific binder (e.g. an antibody) to each protein, and then produce an array with each of those specific binders immobilized thereon. Such prior art methods were time-consuming and labor-intensive and presupposed an advanced knowledge of the identity of individual proteins within a sample in order to generate a specific binder for each protein.

The present invention has overcome these disadvantages. For example, no advanced knowledge of the identity of individual proteins in a protein sample is required in order to perform the method of the present invention because a standard array of binders can be used for any sample. Moreover, much lower numbers of different binders are required than the methods employed by the prior art. This is because the present invention employs binders that can each bind to peptides and protein and peptide fragments from divergent sources. Since the binders used in the present invention are not specific for an individual protein source, they can each bind multiple unrelated protein and peptide fragments. Accordingly, a less than 1:1 ratio between binders and proteins in a sample can be utilized. This makes the production and use of arrays much more economical and labor-efficient than those required to implement the prior art methods.

The present invention overcomes the disadvantages of the prior art methods by a unique interrelationship between the binding and characterizations steps. The binding steps of the present invention involve separating peptides, or protein or peptide fragments, into distinct classes irrespective of the parent proteins from which they were derived. The only distinguishing feature of each class is that the molecules bound in any given class will all contain the same motif, e.g. the same C-terminal tri- or tetra-peptide sequence. Thus, the variety of peptides, or protein of peptide fragments bound to a given type of binder can differ

in sequence at all positions other than the common motif, i.e. a heterogeneous class of peptides, or protein or peptide fragments, will be bound to any given type of binding molecule. As a result of this, lower numbers of binders are required in order to capture a useful proportion of peptides, or protein or peptide fragments, in a sample and, moreover, no advanced knowledge of the identity of proteins in a sample is required – on the contrary, a standard array can be used to analyze any sample of proteins.

However, because the peptides, or protein or peptide fragments, bound by each type of binding molecule in the method of the present invention are heterogeneous, their separation during the binding step is incomplete. Such incomplete separation could not be tolerated by those prior art methods that provide for the determination of protein abundance in a sample (e.g., including the prior art reference Barry cited by the Examiner) because they rely on having *homogeneous* classes at each location on an array so as to allow the user to correlate protein abundance at a given array location with the abundance of a specific bound protein.

Alternatively, those prior art methods for protein sample analysis that suggested that heterogeneity (i.e. incomplete separation) could be tolerated following the separation of a sample on an array (e.g., including the prior art reference Minden cited by the Examiner) did not attempt to determine the abundance of the different species bound within the thus-formed heterogeneous classes. Rather, in the case that heterogeneity was tolerated by such prior art methods, it was taught that it was necessary to provide multiple binders at different locations on an array to bind multiple different fragments *from the sample single protein*, in order to create binding patterns on the array that are characteristic of each protein, thereby to identify individual proteins. Such methods did not provide for the determination of abundance.

However, in the case of the present invention, the incomplete separation during the binding step of peptides, and protein and peptide fragments, derived from different parent

proteins (i.e. the creation of heterogeneous classes) can be tolerated in a method that involves the determination of, *inter alia*, the *abundance* of the peptides, or protein or peptide fragments, *in the heterogeneous classes*. This is because the molecules in each class are characterized to determine the different masses of molecules in each class and the relative abundance of molecules of each mass in a given class. Thus, molecules derived from different parent proteins are distinguished on the basis of mass *and* abundance.

By combining the information derived from the binding and characterization steps it is possible to derive a picture of the protein sample analyzed, through a simple and time-efficient method that requires no advanced knowledge of the individual proteins in the sample being analyzed and employs only a single binding affinity step.

2. The Rejections Under 35 U.S.C. §103 Should be Withdrawn

The Examiner has maintained her rejection of Claims 1-11,13-14,17-18, 21 and 24-27 are rejected under 35 U.S.C. §103(a) as being unpatentable over Minden and Barry et al. WO 0225287 ("Barry").

In response to Applicant's arguments that there is no suggestion to combine the references taught by Minden, the Examiner maintains that she recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. According to the Examiner, Barry was utilized in the rejection for motivation which is reiterated along with the reasonable expectation of success statement; (1) one having ordinary skill in the art would have been motivated to do this because Barry teaches that the use of mass spectometry and MALDI-TOF provide semi-quantitative results for protein microarrays and (2) one of ordinary skill in the art would have had a reasonable expectation of success in the modification of the method of identifying proteins taught by Minden with

the MALD-TOF analysis taught by Barry because of the examples provided by Barry showing that trypsin digested antibody arrays can be quantitated via MALDI-TOF.

Applicant submits that the Office has not set forth a *prima facia* case of obviousness. A finding of obviousness under 35 U.S.C. § 103 requires a determination of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed subject mater and the prior art; and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1966).

As set forth in Applicants prior response, the present invention relates to a method for proteomic analysis of a heterogeneous sample of proteins, or protein or peptide fragments by *separating the sample into heterogeneous classes* at spaced apart locations on an array wherein no advanced knowledge of the identity of individual proteins in a protein sample is required in order to perform the method of the present invention.

According to the Examiner, although Minden may not specifically teach determining the abundance of the proteins, Barry provides an abundance determination step to apply to Minden's method. In this regard, Applicants maintain that it is essential to note that Barry only teaches a method of proteomic analysis *wherein each binding reagent corresponds to one protein* or peptide and requires advanced knowledge of proteins in the sample in order to generate an appropriate array of binders. In other words, Barry only teaches the determination of abundance wherein the analysis is applied to *homogeneous* classes of array-bound proteins or peptides. This is contrast to the present invention which relates to a method of determining the mass and abundance of a *heterogeneous class of array-bound peptides, or protein or peptide fragments*. In this regard, Applicants have amended claim 1 to specify that "more than one peptide, protein or peptide fragment binds to each defined location on the array." Applicants maintain that one of skill in the art would not have had a reasonable expectation of success in determining the abundance of a heterogenous class of

polypeptides via MALDI-TOF merely because Barry taught that one could determine the abundance of a homogenous classes of polypeptides using such a method.

Applicants assert that a *prima facia* case of obviousness has not been established. In light of these remarks, Applicant respectfully requests that the obviousness rejections be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is believed that the subject claims are in condition for allowance, which action is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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